REMARKS

Applicants would like to thank Examiners Zohreh Vakili and Ardin Marschel for the courtesy of the telephone interview on July 20, 2010 to the undersigned attorney. Applicants wish to thank the Examiners for their helpful suggestions.

In the Action, the examiner rejected claims 45-55 under 35 USC §112, 1st paragraph as assertedly lacking enablement, and under 35 USC §103(a) as assertedly obvious in view of Nichol et al., US Patent 4,587,340 (hereinafter "Nichol") and JP05194229.

I. Summary of Interview of July 20, 2010 pursuant to MPEP §713.04 and 37 CFR §1.133

During the interview, the outstanding enablement and art-based rejections, and proposed amendments of claim 45, were discussed. No final claim language was agreed upon.

II. Support for the Amendments to the Claims

Support for the amendment to claim 45 is found throughout the specification. For example, the Example at pages 26-38 describes treatment of patients having varying degrees of protein tolerance, e.g., mild phenylketonuria (PKU), mild hyperphenylalaninemia, or classical PKU, with BH4, and describes that patients having a deficiency in BH4 were selectively excluded from the treatment group (page 28). Pages 32-33 and Table 1 teach identification of the mutations in the PAH gene expressed in the patients being treated. The recitation of 5,6,7,8 tetrahydrobiopterin in claim 45 finds support among the compounds in the Markush group of original claim 48. The amendment includes no new matter.

III. The rejection of claims 45-55 under 35 USC §112, 1st paragraph, as assertedly lacking enablement should be withdrawn

The examiner rejected claims 45-55 as allegedly lacking enablement, asserting that the specification failed to teach how to make and use the compounds useful in the claimed methods. The examiner contends that the specification lacks specific conditions or starting material or reaction conditions sufficient to teach one of ordinary skill how to synthesize the claimed compounds. The examiner further states that even if the reaction schemes were taught in the art, the method of synthesis is essential subject matter which cannot be incorporated by reference (page 5 of the action). Applicants respectfully disagree.

The claims as amended recite that the compound is 5,6,7,8 tetrahydropbiopterin or a pharmaceutically acceptable salt thereof.

It is a well accepted principle that "a patent need not teach, and preferably omits, what is well known in the art." See MPEP 2164.05(a); *Hybritech Inc. v Monoclonal Antibodies Inc.*, 802 F. 2d 1367, 1384 (Fed. Cir. 1986). In this case, the synthesis of BH4 and derivatives thereof has been known and described extensively in the published literature for several decades. Moreover, even if a considerable amount of work were required to carry out the invention, when such experimentation is routine, the experimentation is not "undue," In re Wands, 858 F2d 731 (Fed. Cir.1988). "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 561 F2d 220, 224 (CCPA 1977).

During the examiner interview, Examiner Marschel indicated that it would not be necessary to incorporate the synthesis process into the application by amendment, if applicants explained how the synthesis process was well known in the art and provided references in a response. Applicants submit that in light of the commercial availability of tetrahydrobiopterin (BH4) at the time of filing, and in view of the well known synthesis methods described in the references below and generally known in the art, a person of ordinary skill in organic synthesis could readily make BH4 (or a derivative thereof).

BH4 is commercially available from Schircks Laboratories (for lab or pharmaceutical use, see Exhibit A) and BH4 has been used to treat BH4 deficiency for over 25 years (Schirks material, Exhibit A). Thus, the compound itself is well-known, readily available to a person of skill for purchase and has been used as a pharmaceutical for over two decades. Additionally, methods to synthesize tetrahydrobiopterin and other pterin analogs have been known in the art for over 50 years. For example, tetrahydrobiopterin has been prepared by: (1) the reaction of 4-hydroxy-2,5,6-triaminopyrimidine (TAP) and 5-deoxy-L-arabinose as described in E. L. Patterson et al., J. Am. Chem. Soc., 78, 5868 (1956); (2) the reaction of TAP and 5-deoxy-L-arabinose phenylhydrazone, as described in Sugimoto and Matsuura, Bull. Chem. Soc. Jpn., 48, 3767 (1975); (3) the reaction of TAP and triacetyloxy-5-deoxy-L-arabinose phenylhydrazone, as described in Schircks et al., Helv. Chim. Acta., 60, 211 (1977); (4) the reaction of oxime and benzyl α-aminocyanoacetate and condensation of the resulting 3-(1,2-dihydroxypropyl)-pyrazine-1-oxide derivatives with guanidine followed

by deoxygenation of the N-oxide, as described in E. C. Taylor et al., J. Am. Chem. Soc., 96, 6781 (1974); (5) the reaction of α-hydroxyketone (prepared from crotonic acid) and TAP, as described in M. Viscontini et al., Helv. Chim. Acta., 55, 574 (1972); and (6) the reaction of TAP having protected hydroxyl group and 4-acetoxy-2,3-epoxypentanal followed by oxidation with iodine and deprotection, as described in Sugimoto et al., Journal of Synthetic Organic Chemistry, Vol. 46, No. 6, p. 564 (1988), by protecting the hydroxyl group of S-alkyl lactate with a trityl group, reducing the resulting alkyl 2-trityloxypropionate to (S)-2-trityloxypropanol, oxidizing it to (S)-2-trityloxypropanal, treating it with a 2-furyl metal compound to form (1S, 2S)-1-(2-furyl)-2-trityloxy-1-propanal followed by oxidation and hydrolysis to form 2,3-dideoxy-6-trityloxyhepto-2-enopyranose-4-ulose, reducing it to 6-trityloxyhepto-2-ene-1,4,5-triol, acylating it to from 1,4,5-triacyloxy-6-trityloxyhepto-2-ene followed by oxidation to afford 2,3 diacyloxy-4-hydroxy-1-pentanal, treating it with phenylhydrazine to from a hydrazine, and condensing the hydrazine with a 3,5,6-triaminopyrimidinol followed by oxidation and deacylation, as described in Japanese Kokai No. 221380/1989. The references above are provided in the accompanying information disclosure statement and SB/08 form. Using the methods described above, some of which have been available for over 50 years, one of ordinary skill in the art can readily obtain BH4.

BH4 starting material is readily available commercially or via the synthesis methods described above. US 4,665,182 discloses that BH4 has been used to treat Parkinson's disease (referencing a 1982 article) and describes that BH4 at that time was expensive to purchase (col. 3, lines 2-9), further supporting the suggestion that BH4 was readily available and processes for synthesis of the compound were known in the art. Additionally, the 6R stereoisomer of tetrahydrobiopterin, sapropterin, also known as BIOPTEN, was available commercially from Suntory Pharmaceuticals (page 24 of the English specification).

The examiner acknowledges that the art had provided a detailed blueprint for making and using modified compounds of the general formula as claimed, the sequence of which is provided by Nichol and JP05194229, and the steps of which are routine to one of ordinary skill (page 13 of the Action). One of ordinary skill in the art of chemical synthesis would readily recognize that the compounds recited in the claims are made using standard chemical synthesis techniques as disclosed in the art, e.g., the numerous articles cited above.

Thus, the tetrahydrobiopterin compounds recited in the claim and methods of making them have been known in the art for many years, and methods of making these compounds and derivatives thereof using routine chemical synthesis methods have been taught in the art, as acknowledged by the examiner.

The examiner argues that even if one of ordinary skill could have made the compounds recited in the claims based on knowledge in the art, the manner of making them is essential subject matter which cannot be incorporated by reference. However, material is only essential if ***"one skilled in the art could not develop [the missing information] without undue experimentation*** *(emphasis added).* Applicants submit that in the present case, synthesis procedures for the compounds in Formula I recited in the claims has been known for over 50 years and has been ***routine*** for over 15 years, see e.g., EP 0164964 and US 4,665,182, and any of the numerous articles cited above, such that reproducing exact chemical reaction schemes in the specification is not necessary and essential to enable synthesis. Such well known material is not essential, need not be included and, in fact, is ***preferably omitted.*** See MPEP 2164.05(a). Additionally, what is commonly known in the art need not be included in the specification (See Hybritech v Monoclonal Antibody, Inc., *supra*).

The level of skill in the art of making tetrahydrobiopterin and its analogs useful in the present methods is high, and methods to make these compounds have been well-known in the art for several decades and need not be included in the specification. One of ordinary skill in organic synthesis could have readily made the compounds for use in the claimed methods using any of the several methods described above as well as the general knowledge in the art without undue burden, and therefore, the material is not essential to enablement of the specification. The compounds of claim 45 and 48 were commercially available prior to the filing date of the present application and have been synthesized by artisans for several decades. Under MPEP 2106, each claim should be reviewed for compliance with the statutory requirements

For all of the reasons described above, the specification is sufficiently enabled such that one of ordinary skill can carry out the methods of the invention and the rejection of the claims as lacking enablement should be withdrawn.

IV. The rejection of claims 45-55 under 35 USC §103 should be withdrawn

The examiner rejected claims 45-55 as allegedly obvious in view of Nichol and JP 05194229, asserting that one of ordinary skill would have readily modified the teachings of Nichol and JP05194229 to arrive at the present method for treating conditions of reduced protein tolerance using the recited compounds. Applicants respectfully disagree.

The claims are directed to a method of treating conditions in a patient with lowered protein tolerance due to reduced phenylalanine oxidation without deficiency of cofactor tetrahydrobiopterin (BH4), wherein the patient has been identified as having a specified mutation in the phenylalanine hydroxylase gene, and wherein the agent used is of the formula recited in the claims. 5,6,7,8-tetrahydrobiopterin (BH4) is an exemplary compound useful in the methods of the invention.

To establish a *prima facie* case of obviousness, the Examiner must show that all the elements of the claim are taught or suggested in the prior art, or reasoned from general knowledge in the art (MPEP §2144 and Federal Register Examination Guidelines for Determining Obviousness, Section III.A.1, Fed Reg., Vol 72, No. 195, 2007). If all the elements are described in the art, the combination of elements must yield predictable results to render a claimed invention obvious. Further, it should be demonstrated that the prior art reference(s) provide a teaching, suggestion or motivation to combine the references, and/or there is a reasonable expectation of success (MPEP §2142 and Federal Register Examination Guidelines for Determining Obviousness, Section III.G, Fed Reg., Vol 72, No. 195, 2007). The Court in *KSR v Teleflex* (127 S.Ct. 1727 (2007)) further stated that mere conclusory statements are not sufficient to draw a conclusion of obviousness, but that there must be some articulated reasoning with some rational underpinning to support a legal conclusion of obviousness. See Fed Reg., Vol 72, No. 195, Pages 57529 and KSR v Teleflex, 127 S.Ct. 1727.

The examiner has failed to establish a *prima facie* case of obviousness since all the elements of the claimed invention are not disclosed in the cited art. Moreover, there is no motivation to combine the teachings of Nichol and JP05194229 to arrive at the present invention, nor is there a reasonable expectation of success that one of ordinary skill would have arrived at the present invention based on the teachings in the art.

Nichol discloses use of pterin analogs, which are analogs of BH4, and use of these analogs to treat Parkinsonism and BH4 deficiency. Patients with BH4 deficiency are unable to synthesize or recycle adequate amounts of BH4. In contrast, patients with PAH mutations have a defective PAH enzyme that is unable to degrade phenylalanine efficiently, thus resulting in elevated levels of phenylalanine in blood and consequently elevated levels of phenylalanine excreted into urine. Nichol neither discloses nor suggests that BH4 would be beneficial to treat a patient with a protein tolerance disorder identified as resulting from a mutation in the PAH gene, which is a different basis for disease compared to BH4 deficiency.

JP05194229 discloses use of a pterin agent to treat nervous diseases, such as concentration disorders, akinesia, shivering, etc. The agents in JP05194229 are similar to those agents recited in the claimed method. However, JP05194229 neither discloses nor suggests that the pterin agents are useful to treat any disorder other than a nervous disorder, let alone treat a protein tolerance disorder resulting from a mutation in the PAH gene and not from BH4 deficiency.

Neither Nichol nor JP05194229, taken alone or in combination, discloses treatment of a protein tolerance disorder in a patient identified as having a mutation in the PAH gene. Moreover, neither Nichol nor JP05194229 disclose the specific pairs of PAH mutations recited in claim 45 or their correlation with sensitivity to and efficiency of BH4-based treatment of protein intolerance due to PAH mutations.

Further, one of ordinary skill in the art would not have been motivated by the cited art, nor had a reasonable expectation of success based on the cited art, to arrive at the present invention. Neither Nichol nor JP05194229 describe what role BH4 would play in correcting any mutation in the PAH gene, much less the mutations recited in the claims. Thus, the cited art does not motivate one of ordinary skill to treat these mutations with BH4 or provide a reasonable expectation of success for doing so.

During the interview, the examiners appeared to recognize that the cited art did not disclose correlation of BH4 treatment with the PAH mutations recited in the claims. Applicants thank the examiners for their suggestion to amend the claims to recite that the mutations had been identified in the patients being treated with BH4, and believe that the amendment and remarks herein fully address the examiners' concerns.

For the foregoing reasons, the rejection of claims 45-55 as obvious in view of Nichol and JP05194229 should be withdrawn.

V. Conclusion

Applicants submit that the present application is in condition for allowance and respectfully request notification of the same.

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Respectfully submitted,

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